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BMJ Open Decreasing the load? Is a Multidisciplinary Multistep Medication Review in older people an effective intervention to reduce a patient's Drug Burden Index? Protocol of a randomised controlled trial

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ABSTRACT

Introduction: Older people often use medications with anticholinergic or sedative side effects which increase the risk of falling and worsen cognitive impairment. The Drug Burden Index (DBI) is a measure of the burden of anticholinergic and sedative medications. Medication reviews are typically done by a pharmacist in collaboration with a general practitioner to optimise the medication use and reduce these adverse drug events. We will evaluate whether a Multidisciplinary Multistep Medication Review (3MR) is an effective intervention to reduce a patient's DBI.

Methods: A randomised controlled trial including 160 patients from 15 community pharmacies will be conducted. Per pharmacy, 1 pharmacist will perform a structured 3MR in close collaboration with the general practitioner, including the objective to reduce the DBI.

Analysis: Primary outcome—the difference in proportion of patients having a decrease in $DBI \geq 0.5$ in the intervention and control groups at follow-up. Secondary outcomes—anticholinergic and sedative side effects, falls, cognitive function, activities of daily living, quality of life, hospital admission, and mortality.

Ethics and dissemination: The burden of patients will be kept at a minimum. The 3MR can be considered as usual care by the pharmacist and general practitioner. Medical specialists will be consulted, if necessary. The intervention is specifically aimed at older community-dwelling patients in an attempt to optimise prescribing, in particular, to reduce medication with anticholinergic and sedative properties. Study results will be published in peer-reviewed journals and will be distributed through information channels targeting professionals.

Trial registration number: NCT02317666; Pre-results.

INTRODUCTION

Older individuals use more medications than any other age group.¹ They typically suffer from multiple acute and chronic diseases,

which often necessitates the use of multiple concomitant medications.² Polypharmacy in combination with age-related pharmacokinetic and pharmacodynamic changes, such as decrease in renal function and altered drug responsiveness, predisposes older individuals to an increased risk of drug–drug interactions, drug–disease interactions, adverse drug events and potentially inappropriate prescribing (PIP).^{3–5} Many PIP instances are attributable to medication with anticholinergic and/or sedative properties.^{6,7} Those medications increase the risk of falls in older people and worsen cognitive impairment, resulting in problems in activities of daily living (ADL).^{8–11} Around 600 medications are known to have anticholinergic effects to a greater or lesser extent,¹² and many of these are widely used among older people, especially cardiovascular medication^{13,14} and medicines acting on the central nervous system. Hypnotics and sedatives are among the most commonly used psychotropic medications, especially in the very old.¹⁵ A Finnish study found that almost one-third of adults aged >75 years used anxiolytic or hypnotic medication, and almost one-tenth used antidepressant or antipsychotic medicines.¹⁶ Given these findings, decreasing the exposure to anticholinergic and sedative medications is likely to result in important health benefits for older people. The Drug Burden Index (DBI) calculates an individual patient's exposure to anticholinergic and sedative medications taking into account the medicine dosage.¹⁷ A recent literature review shows that the DBI is associated with impairments in physical and cognitive functions of older individuals.^{18,19}

Medication reviews are seen as a promising strategy to enhance the quality of prescribing, although there is still a lack of evidence on cost or clinical effectiveness. Medication reviews could be made more effective by targeting high-risk groups and focusing on medicines which could be safely stopped.^{20–23} According to Dutch guidelines, a medication review is a structured critical examination of a patient's medication, done by a pharmacist and a general practitioner (GP), to reach an agreement with the patient about treatment, optimising the effectiveness of the medicines, and minimising the number of medication-related problems.²⁴ Annual Multidisciplinary Multistep Medication Reviews (3MR) are recommended for older chronic polypharmacy patients with additional risk factors. However, criteria used so far—living in a nursing home, decreased renal clearance (estimated glomerular filtration rate <50 mL/min/1.73 m²), decreased cognitive function, increased risk of falling, signals of decreased medication adherence or unplanned hospital admission²⁴—form an inadequate demarcation of the high-risk population. Therefore, in the present study, we used the DBI to identify high-risk patients who could benefit from medication reviews. The aim of our study is to evaluate whether a 3MR is an effective intervention to reduce a patient's DBI.

METHODS AND ANALYSIS

Study design

A single-blinded randomised controlled trial will be conducted in line with the 'Consolidated Standards of Reporting Trials (CONSORT)' statement ([https://www/consort-statement.org](https://www.consort-statement.org)) and the 'Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)' criteria (<https://www.spirit-statement.rug>). Patients will be recruited from pharmacies and will be randomly allocated into control group and intervention group (refer to Selection process, randomisation, intervention allocation and blinding section). The intervention consists of a 3MR conducted by the pharmacist in collaboration with the GP. The main aim of the medication review is to optimise the patient's medication with a focus on lowering the DBI by reducing medication with anticholinergic and sedative properties. Participants in the control group will receive the 3MR after the study period (postponed intervention). Primary and secondary study outcomes will be determined for intervention group and control group at baseline and at 3 months of follow-up after the intervention.

Participants and setting

Our aim is to enrol a minimum of 160 participants from 15 community pharmacies in the region of Groningen, the Netherlands (see Sample size calculation section). We will approach a total of 400 patients to recruit about 160 participants. One pharmacist will conduct the medication reviews in each pharmacy. As one community pharmacy is mostly associated with several medical

practices, the pharmacist will collaborate with different GPs, but with only one GP for each patient.

Pharmacists

Inclusion criteria

- ▶ Established collaboration with the GP
- ▶ Experience with medication reviews (accredited community pharmacist or registered pharmacist in training to be accredited).

Participants

Inclusion criteria

- ▶ Aged ≥ 65 years
- ▶ Living independently
- ▶ Chronic polypharmacy (≥ 5 medications for ≥ 3 months²⁴ and DBI ≥ 1)
- ▶ Use of at least one medication with ATC N05 or N06
- ▶ Written informed consent (IC)

Exclusion criteria

- ▶ Palliative care only
- ▶ Limited life expectancy (< 3 months)
- ▶ Urgently in need of a medication review
- ▶ No Dutch language skills
- ▶ Advanced dementia
- ▶ Received a medication review within 9 months before the study period.

Sample size calculation

A minimum of ~160 participants (80 in the control group and 80 in the intervention group) will be sufficient to detect a medium effect size with a power of 80%, an α of 5% on the primary outcome, and an intra-class correlation coefficient up to 0.2.²⁵ To the best of our knowledge, only one pilot randomised study has been conducted that was aimed at decreasing the DBI.²⁶ We, therefore, cannot estimate an effect size 'a priori' as this should be based on multiple independent studies. Since a small effect size will probably be clinically irrelevant and a large effect size may be unrealistic, we chose a medium effect size. With the aim to include 160 patients and the expectation of a non-response rate of 60%, we will invite a total of 400 participants.

INTERVENTION

The intervention will be a 3MR carried out by the pharmacist in close collaboration with the GP and if needed, with medical specialists. The medication reviews will be based on current Dutch guidelines with a focus on lowering the load of anticholinergic/sedative medication following five steps as outlined below.²⁴ Pharmacy students will be assisting the community pharmacists during some steps of the reviews. Participants in the control arm will receive their medication review after the follow-up measurement. All participants have been informed about the possible delay of their medication review as part of the IC procedure.

Step 1: pharmacotherapeutic anamnesis

The pharmacist collects information about the actual medication use, problems with the medication use, and experiences, efficacy and possible side effects of the medication—in particular anticholinergic and sedative medication—during a face-to-face consultation with the patient. Furthermore, the use of ‘over-the-counter’ medication, and patients’ expectations and preferences about their medication will be discussed.

Step 2: pharmacotherapeutic medication review

The pharmacist identifies potential pharmacotherapeutic problems considering the patient’s characteristics and experiences, life expectancy, and preferences using PIP tools such as the STOPP and START criteria.⁶ The pharmacist will draft recommendations for the GP. Different problems and/or recommendations will be prioritised. Recommendations could include to start or stop medication, change doses or carry out additional laboratory tests.

Step 3: multidisciplinary meeting

The pharmacist discusses the patient’s medication profile with the GP during a face-to-face meeting. Together, they will draft an action plan, including treatment objectives, potential actions, and priority of actions (eg, withdrawing medication). Preferences of the patient, patient characteristics, experience, and life expectancy will be central in the decision-making process. If needed, the appropriate medical specialists will be included in the medication review.

Step 4: pharmaceutical action plan

The pharmacist or GP discusses the action plan, made in step 3, with the patient. An agreement about the action plan will be made with the patient, preferences, expectations and concerns of the patient are key points in the decision-making process. Time schedule for the next intervention will be made and changes in medication treatment will be registered.

Step 5: follow-up

Actions made in step 4 are evaluated at an agreed time interval with the pharmacist and/or GP.

Study parameters**Main study parameter**

The key aim of the 3MR is to optimise a patient’s medication and to lower the DBI by reducing medications with anticholinergic and sedative properties. The DBI will be measured for all participants at baseline and follow-up using electronic pharmacy dispensing records corrected for actual medication intake based on a

double check with the patient by telephone. We will calculate the DBI using the following formula:

$$DBI = \sum \frac{D}{D + \delta}$$

D, daily dose of a drug; δ , minimum recommended daily dose as stated in Dutch standard reference sources.²⁷

All chronically used (≥ 3 months) medications (excluding dermatological (ATC D) and sensory medication (ATC S)) having anticholinergic properties (including dry mouth, constipation and urine retention) or sedative properties based on standard Dutch reference sources^{27–30} will be included in the calculation. For each drug, the value of the DBI will range from 0 to 1 depending on the δ . The cessation of one anticholinergic or sedative medication would lower the DBI by about 0.5. We consider the cessation of one drug to be clinically relevant and therefore, defined the primary outcome as the difference in proportion of patients having a decrease of $DBI \geq 0.5$ from baseline to follow-up in the intervention group and in the control group. It is expected that at follow-up, the proportion of patients with a decrease of the $DBI \geq 0.5$ is significantly higher in the intervention group in comparison to the control group.

Secondary parameters

Secondary study parameters are chosen with regard to patient outcomes. All questionnaires and tests will be administered to all participants at baseline and follow-up (see Study procedures section).

- ▶ Anticholinergic side effects: as measured by the Undersøgelsesr (UKU) side effect rating scale.³¹
- ▶ Sedative side effects derived from a patient-reported adverse drug event questionnaire.³²
- ▶ Risk of falls: as measured by patient-reported fall incidents and the ‘Up & Go’ test.³³
- ▶ Cognitive function: as measured by the ‘Seven Minute Screen’,³⁴ the ‘Trailmaking Test A & B’³⁵ and the ‘Digit Symbol Coding Test’ of the ‘Wechsler Adult Intelligence Scale III’.³⁶
- ▶ ADL: as measured by the ‘Groningen Activiteiten Restrictie Schaal’.^{37 38}
- ▶ Quality of life: as measured by the EQ-5D-3L questionnaire.³⁹
- ▶ Hospital admission: assessed from the patient’s medical records.
- ▶ Mortality: assessed from the patient’s medical records.

Covariates

All demographic characteristics (sex, age, educational level, marital status), and number of medications at baseline and follow-up will be included in the analysis.

Selection process, randomisation, intervention allocation and blinding

A preliminary list of potentially eligible patients will be obtained by electronic search in the electronic pharmacy dispensing records based on a limited set of inclusion criteria (age, chronic polypharmacy, use of psychotropic medication (NO5/NO6)). Notably, patients in the Netherlands are registered with one pharmacy, so the pharmacies keep relatively accurate dispensing records of all prescribed medication. Inclusion/exclusion criteria will be checked by the researchers, pharmacists and GPs to obtain a list of eligible patients who will be approached for IC as outlined below. Within each pharmacy, all included patients will then be matched in pairs by gender, age, DBI and number of medications. Subsequently, this list of participants will be sent to the principal investigator (KT) who is not involved in the recruitment and data collection. Within each pair, one participant will be randomly assigned to the intervention condition by the principal investigator (coin flipping). The principal investigator will inform the pharmacists about the patient's allocation. Pharmacists and participants cannot be kept blind. All researchers involved in data collection will be kept blind to the allocation. Therefore, this is a single-blinded study. This method will ensure that we have balanced groups within each pharmacy, random allocation, and concealment of allocation from the researchers involved in data collection. Pharmacies will be enrolled continuously, and all participants of one pharmacy will be enrolled at the same time. This excludes other methods such as stratified randomisation of all participants at the same time.

Quality of data

We will collect data in a standardised manner using data collection sheets. All researchers will be trained by an experienced neuropsychologist. We will assess patients' cognitive function using objective and validated neuropsychological tests (see Study parameters section). Validated questionnaires will be used to assess anticholinergic and sedative side effects, loss of ADL, and quality of life (see Study parameters section). Medication data will be collected from the pharmacy information system and actual use will be verified by the patient. All data will be entered in a Microsoft Access database by a research assistant. Baseline data will be collected before the intervention. Follow-up data will be collected 3 months after the intervention has taken place, assuming that within these 3 months the maximum effect of possible medication changes made during the 3MR are reached. All data entries will be double-checked against hardcopy source data.

Statistical analysis

All data will be analysed in IBM SPSS V.22. Descriptive statistics of the intervention group and control group will be conducted. Analyses will be done 'per protocol' and 'intention-to-treat'. Percentages and frequencies will

be calculated for nominal variables, median values and IQRs, or frequencies will be calculated for ordinal data or continuous data with a skewed distribution. Means and SDs will be calculated for continuous data that follow a normal distribution. Missing data will be kept at a minimum by standardising and monitoring data collection. In case of missing data, sensitivity analyses will be conducted to examine the influence of missing data on the study findings. All statistical tests will be one sided. p Values ≤ 0.05 will be considered significant.

Primary study parameters

Generalised linear mixed models will be employed to account for dependence of data (patients within pharmacy). Consequently, a random intercept and a random slope at the level of pharmacies will be entered into the linear mixed model. Furthermore, we will adjust for significant covariates.

Secondary study parameters

Secondary study parameters will be examined in a similar way. Depending on whether these are continuous variables and their distribution is normally or Poisson distributed, we will employ standard linear mixed models or Poisson linear mixed models.

Study procedures

The flowchart of [figure 1](#) provides a schematic overview of the study phases along with the participant flow at each study phase.

ETHICS AND DISSEMINATION

The ethics and dissemination are in line with a similar study.⁴⁰ The study will be conducted according to the Declaration of Helsinki regarding the Ethical Principles for Medical Research Involving Human Subjects (amended by the 64th World Medical Association's General Assembly, Fortaleza, Brazil, October 2013), and in accordance with Dutch medical-ethical legislation. The community pharmacist will ask her/ his patients to participate. Prior to participation, written IC will be asked. The 3MR will be based on expert consensus and the medical literature. Moreover, the 3MR will result in high-quality treatment recommendations that will be attained by the pharmacist and treating GP working in close collaboration. Final treatment decisions, however, always rest with the treating GP. We, therefore, argue that our intervention is one of usual care based on the latest evidence-based principles and recommendations made in the guidelines by the Dutch society of General Practitioners.²⁴ The intervention is specifically aimed at older community-dwelling pharmacy patients in an attempt to optimise prescribing and for this study, in particular, to reduce medication with anticholinergic and sedative properties.⁴¹ Data will be handled and stored. To ensure participants' confidentiality, research data and participants' personal data will be stored in two

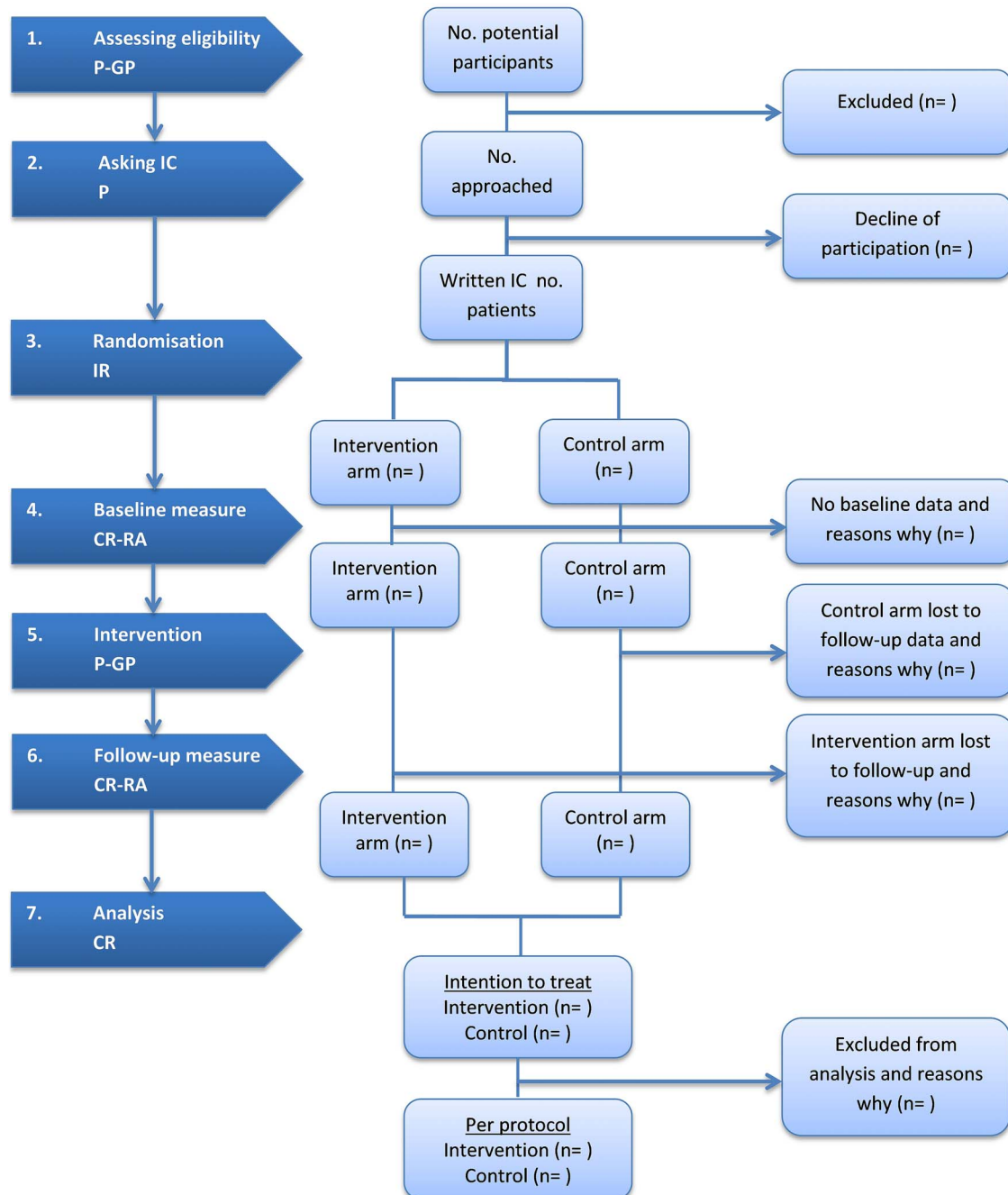


Figure 1 Flowchart study phases and participants (CR, coordinating researcher; GP, general practitioner; IC, informed consent; IR, investigational researcher; P, pharmacist; RA, research assistant).

different files. Data records from both files will be linked with an identification number that cannot be traced to the individual patient and their personal characteristics. The file with patients' personal data will be password protected and will be safeguarded by the investigators. To avoid scientific fraud or misconduct, all investigators will have full access to the data.

Finally, study results will be published in peer-reviewed journals and in newsletters for pharmacists, news messages for the public, and on websites for professionals. If possible, data will be published in open-access articles or as full-text post prints in order to

make them available to the public. Duplicate publication will be avoided.

In addition, this study has been registered at <http://www.ClinicalTrials.gov> (trial registration number: NCT02317666).

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Contributors HGvdM, HW, RvH, NP and KT contributed to the study conception and design; and to the intervention development. HGvdM, HW and KT reviewed the study parameters and contributed to the analysis plan; obtained ethical approval; and drafted the manuscript. All the authors revised and approved the final manuscript.

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Competing interests None declared.

Ethics approval Medical Ethical Committee of the University Medical Centre of Groningen (protocol number METc 2014/392; in Dutch: Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen (METc UMCG)).

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